Substance Group: **Group 28 - Phenol, Heptyl Derivatives**

Summary Prepared by: **Petroleum Additives Panel**
Health, Environmental and Regulatory Task Group

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PHYSICOCHEMICAL PROPERTIES

1.0 Octanol/Water Partition Coefficient

Robust Summary 28-Octanol-1

CAS No.	72624-02-3
Test Substance Name	Phenol, heptyl derivatives
Method/Guideline	n-Octanol/Water Partition Coefficient, OECD Method 117
GLP (Y/N)	*Not Specified*
Year (Published)	1998
Remarks for Test Conditions	Method involved high performance liquid chromatographic (HPLC) correlation analysis using a reverse phase column. The mobile phase consisted of 70% methanol/30% distilled water with a flow of 1 mL/minute at ambient temperature. Reference materials included: 2-ethylphenol, 2-npropylphenol, naphthalene, biphenyl, phenanthrene and fluoranthenc. The reference and test material were dissolved in methanol (0.1-0.3 mg/mL) and duplicate (5 uL) aliquots were applied to the column. The effluent was monitored at 254 and 270 nm. All reference materials and the test substance had a purity of at least 97%. A calibration curve was prepared on the basis of published K_{ow} values for the reference materials and their retention in the HPLC column, expressed as the capacity factor (k) according to the OECD Guideline.
Results	The HPLC correlation analysis revealed that the test material is moderately hydrophobic with a log K_{ow} of 4.5.
Conclusions	The n-octanol/water partition coefficient (log K_{ow}) was 4.5.
Data Quality	Reliable without restriction (Klimisch Code)
References	Tollefsen *et al.* "Acute Toxicity and Toxicokinetics of 4-Heptyl phenol in Juvenile Atlantic Cod (Gadus Morhua L.). Environmental Toxicology and Chemistry, Volume 17, No. 4, 740-746 (1998).
Prepared	September 5, 2003

ENVIRONMENTAL FATE

2.0 Biodegradation

Robust Summary 28-Biodeg-1

Test Substance	
CAS #	CAS# 72624-02-3
Chemical Name	Phenol, heptyl derivatives
Method	
Method/Guideline Followed	OECD 301B, Ready Biodegradability, Modified Sturm Test; ASTM D 5864-95
Test Type (aerobic/anaerobic)	Aerobic
GLP (Y/N)	Y
Year (study performed)	1997
Contact time (units)	28 days
Test apparatus	*Glass 4-liter Erlenmeyer flasks*
Inoculum	Activated sewage sludge from a domestic wastewater treatment plant prepared with soil filtrate per test guideline. Three cultures/group were prepared. The final combined volume of test medium, test substance and inoculum in each test container was 3 liters. Solutions were continuously aerated with CO_2 free air. The test substance was incrementally added at concentrations of 4, 8 and 8 mg C/L on days 0, 7 and 11. On day 14 equal volumes of each culture were combined and the composite inoculum screened and homogenized. A standard plate count was performed on the inoculum. Plates were incubated at 20±3°C for approximately 48 hours.
Cultures/replicates:	*Three replicate test cultures, three replicate blank control cultures and three reference control cultures.*
Temperature of incubation:	20±3°C
Dosing procedure:	Neat test chemical was gravimetrically added to glass cover slips, which were then added to culture medium in test vessels.
Study initiation:	Test flasks provided with CO_2 free air and mixed with a magnetic stirrer. The CO_2 produced from the degradation of organic carbon sources within each test chamber was trapped as K_2CO_3 in 0.5 N KOH and measured using a carbon analyzer.
Sampling:	Days 2, 5, 11, 13, 16, 18, 23 and 29 (after acidification on day 28)
Concentration of test substance:	10 mg C/L weighed directly onto tared glass slides and placed into each test substance flask.
Controls:	Blank and positive controls used per guideline. Positive control was canola oil added to control vessels at a loading of 10 mg C/L.
Analytical method:	The CO_2 produced from the degradation of organic carbon sources within each test chamber was trapped as K_2CO_3 in 0.5 N KOH and measured using a carbon analyzer.

Study termination:	On day 28 the pH of the content of each test flask was determined. The flasks were then acidified with 3 ml of concentrated hydrochloric acid to drive off inorganic carbonate. The chambers were aerated overnight and then the trapping solutions closest to the test chambers were analyzed for inorganic carbon.
Method of calculating biodegradation values:	Percent biodegradation calculated as percent ratio of cumulative net carbon dioxide to theoretical carbon dioxide as determined from elemental analysis of the test material.
Results	The test substance was not considered readily biodegradable under the criteria that requires 60% biodegradation within 28 days, achieved within 10 days of reaching 10% biodegradation. The CO_2 production from the reference chemical exceeded the 60% of theoretical necessary to consider the test valid.
Degradation %	Test substance: 25.4 $\pm$ 1.4 % in 29days (average final pH 7.1) Positive control substance: 91.5 $\pm$ 0.8 % in 29 days
Conclusions	The test substance was not readily biodegradable.
Data Quality	Reliable without restriction. (Klimisch Code)
References	Confidential business information
Other	Updated: 5/27/2003

AQUATIC TOXICITY

3.0 Acute Toxicity to Fish

Robust Summary 28-Fish-1

Test Substance	
CAS #	CAS# 72624-02-3
Chemical Name	Phenol, heptyl derivatives
Remarks	Minimum of 97%
Method	
Method/Guideline followed	Similar to OECD Guideline for Testing of Chemicals #203, Fish Acute Toxicity Test (1984).
Test Type	Acute Toxicity to Fish (flow through test conditions)
GLP (Y/N)	Not specified
Year (Study Published)	1998
Species/Strain	Atlantic Cod
Fish Number	21/concentration (7/replicate)
Fish Size	Average weight 1.1 g
Analytical Monitoring	Not specified
Nominal Test Substance Concentration Levels	Vehicle Control (methanol treated water), 0.5, 1, 2.1 and 4.2 umol/L
Test Concentration Preparation	Not Described
Exposure Period	168 hours
Exposure Conditions	Flow through test conditions.
Vehicle	Methanol
Statistical Analysis	ANOVA, Mann-Whitney U test
Dose Rangefinding Study	No
Test Chambers	1.5-liter glass aquaria
Diluent Water	Temperature: 9.7 ^{o}C Salinity: 32.7 Oxygen Saturation: 89% pH: 8.1
Photoperiod	12-h light per day, 50 Lux.
Positive Control	No
Remarks field for test conditions	Pretreatment: none, fish held for a minimum of 14 days before testing. No feeding 24 hours prior to and during the test. All organisms were observed for mortality twice daily
Results	Cumulative mortality (%) was as follows:

	% Cumulative Mortality (n=21)						
Nominal Concentration (umol/L)	0 hours	48 hours	72 hours	96 hours	120 hours	144 hours	168 hours

	0 0 0 0 0 0 0 0 0.5 0 0 5 5 5 5 2 1 0 0 0 0 0 0 0 2.1 0 0 0 10* 10* 14* 19* 4.2 0 5 67* 100* - - - *=Significantly different from control $p \leq 0.05$. The maximum nominal concentration causing no mortality was 1.0 umol/L. The minimum concentration causing 100% mortality was 4.2 umol/L. The 96 hr LC50 was estimated by graphical interpolation to be 2.9 umol/L. No mortality was observed in the vehicle control (methanol/water) group.
Conclusions	The 96 hr LC50 was 2.9 umol/L. The 96 hour NOEC was 1 umol//L.
Data Quality	Reliable with restriction (Klimisch Code). Restriction due to lack of analytical confirmation of test material concentration.
References	Environmental Toxicology and Chemistry, Volume 17, No. 4, 740-746 (1998).
Other	Updated: September 5, 2003

3.1 Acute Toxicity to Aquatic Invertebrates (e.g. Daphnia)

Robust Summary 28-DAPH-1

Test Substance	
CAS #	72624-02-3
Chemical Name	Phenol, heptyl derivatives
Remarks	Purity not provided
Method	
Method/Guideline followed	OECD Guideline for Testing of Chemicals #202 Daphnia sp. Acute Immobilization Test and Reproduction Test (1984).
Test Type	Static acute toxicity test
GLP (Y/N)	Y
Year (Study Performed)	2005
Species/Strain	Daphnia magna
Analytical Monitoring	Concentration and stability at 0 and 48 hours
Exposure Period (unit)	48 hours
Positive Control	Potassium dichromate at 0, 0.32, 0.56, 1.0, 1.8, 3.2 mg/L (conducted every 6 months).
Statistical methods	EC50 values calculated using the trimmed Spearman-Karber method (ToxCalc software 1999).
Remarks field for test conditions (fill as applicable)	Twenty-four hour old Daphnia magna derived from in house cultures were used for the study. 50 mg of test material was dispersed in reconstituted water (500 mL). These dispersions were shaken at 300 rpm at 30°C for a period of 24 hours. The flasks were then cooled to 21°C and the undissolved test material removed by filtration (0.2 µm filter) through a preconditioned filter and pooled to give a nominal concentration of 30 mg/L. Aliquots of this solution were dispersed in a final volume of 2 liters of reconstituted water to give the remainder of the test series. The test chambers were covered, 250 ml vessels that contained 200 ml of test solution. Ten daphnids/time point were distributed into each concentration for the range finding study. Ten daphnids/replicate/time point (2 replicates) were used in the definitive study. Test vessels were covered to reduce evaporation and were maintained at 20.7 to 21.1°C with a photoperiod of 16 hours light and 8 hours dark. Daphnia were not fed nor were cultures aerated during exposure. Control groups were handled in the same manner as the test groups. Test preparations were not renewed during the exposure period. Water temperature was recorded daily throughout the test. Dissolved oxygen concentration and pH were recorded at the start and end of the study. Any immobilization or adverse reactions to exposure were recorded at 24 and 48 hours after the start of exposure. Daphnia were considered immobilized if they were unable to swim for approximately 15 seconds after gentle agitation.
Test Concentrations	Range Find Study: 0, 0.030, 0.30, 3.0 mg/L (nominal concentration) Definitive Study: 0, 0.041, 0.059, 0.10, 0.19, 0.30, 0.61, 1.1, 2.0, 3.2 mg/L

	(analytical concentration)
Results	The 24 and 48-hour EC_{50s} (Effective Concentration) were determined to be 0.64 and 0.38 mg/L. The no observed effect concentrations (nominal) after 24 and 48 hours were 0.30 and 0.17 mg/L.
Data Quality	Reliable without restriction (Klimisch Code).
References	Wetton & McKenzie. 2005. Acute Toxicity to Daphnia Magna. SafePharm Project Number 1666/073. 27 Sep 2005.
Other	Updated 11/16/05

3.2 Toxicity to Aquatic Plants (e.g. Algae)

Robust Summary 28-ALG-1

Test Substance	
CAS #	72624-02-3
Chemical Name	Phenol, heptyl derivatives
Remarks	Test material purity not provided.
Method	
Method/Guideline followed	OECD Guideline for Testing of Chemicals #201 Alga, Growth Inhibition Test (1984).
Test Type	Static acute toxicity test
GLP (Y/N)	Y
Year (Study Performed)	2005
Species/Strain	Freshwater algae, *Scenedesmus subspicatus*/CCAP 276/20
Element basis (# of cells/mL)	Approximately 2.05 x 10^6 cells/mL, 5 mL used to inoculate 1 liter of medium for an initial cell density of 10^4 cells/mL.
Exposure period/duration	72 hours
Range find test	Yes
Analytical monitoring	Concentration and stability
Statistical methods	A Students t-test incorporating Bartlett's test for homogeneity of variance and Dunnett's multiple comparison procedure were used to compare the area under the growth curve data of the treated and control groups at 72 hours.
Remarks field for test conditions (fill as applicable)	Test Species: Cultures obtained from the Culture Collection of Algae and Protozoa (CCAP), Institute of Freshwater Ecology, The Ferry House, Far Sawrey, Ambleside, Cumbria, or Dunnstaffnange Marine Laboratory, Oban, Argyll, Scotland. Loading Concentration: Range Find Study: 0, 0.030, 0.30, 30 mg/L Definitive Study: 0, 0.48, 0.095, 0.19, 0.38, 0.75, 1.5 mg/L Test System: 50 mg of test material was dispersed in culture medium (500 mL). These dispersions were shaken at 300 rpm at 30°C for a period of 24 hours. The undissolved test material was then removed by filtration (0.2 µm filter) through a preconditioned filter and pooled to give a nominal concentration of 30 mg/L. Aliquots of this solution were dispersed to give the remainder of the test series. Test Conditions: A static test was conducted; i.e., there was no daily renewal of test solution. Two (range find study) or three (definitive study) 100-mL replicates per treatment, inoculum ~10,000 cells/mL. The 250-mL conical flasks were plugged with polyurethane foam bungs. During the test all treatment and control flasks were randomly placed on an orbital shaker adjusted to approximately 150 cycles per minute under constant light (24 hours/day) for 72 hours. Cell densities were determined using a Coulter Multisizer Particle Counter at 0, 24, 48 and 72 hours. pH was determined at 0 and 72 hours.

	Light: Continuous illumination approximately 7000 lux. Test temperature: 24.0^{o} C. **Culture Media: As specified in the guideline.** Method of determining mean measured concentrations: Solution concentrations were determined a 0 and 72 hours.. Exposure period: 72 hours

Results	Analytical studies confirmed that the test material did not adsorb to glassware and was not volatile. Range Find Study: No effect on growth at 0.030 mg/L however growth was reduced at 0.30, 3.0 and 30 mg/L. Definitive Study: Both growth and biomass were affected by the presence of the test material over a 72 hour period. Based on nominal concentrations: The E_bC_{50} (72 hour), the concentration that reduced biomass by 50%, was 0.25 mg/L. The E_rC_{50}(0-72 hour), the concentration that reduced specific growth by 50%, was 1.2 mg/L. The No Observed Effect Concentration (NOEC) was 0.048 mg/L. The cell concentrations of the control cultures increased by a factor of 42 during the study meeting the guideline requirement of at least a factor of 16 after 72 hours. All test and control cultures were inspected microscopically at 72 hours. No abnormalities were observed in any of the control or treated cultures. Control culture pH increased from 7.3 at 0 hour to 7.9 at 72 hours. Analysis of the test preparations at 0 hours showed measured test concentrations to range from 83 to 101% of nominal. At 72 hours test concentrations ranged from 40 to 67% of nominal. Stability analysis indicated that the test material was stable over 72 hours suggesting that the decline in measured concentration was due to adsorption to algal cells. Given this decline in concentration study results were also calculated based on geometric mean measured test concentration as a worst-case determination. Based on geometric mean measured test concentration: The E_bC_5 (72 hour), the concentration that reduced biomass by 50%, was 0.18 mg/L. The E_rC_{50} (0-72 hour), the concentration that reduced specific growth by 50%, was 0.96 mg/L. The No Observed Effect Concentration (NOEC) was 0.028 mg/L.

Conclusions	Both the growth and the biomass of *Scenedesmus subspicatus* (CCAP 276/20) were affected by the presence of the test material over the 72-hour exposure period. *Based on nominal concentrations:* The E_bC_{50} (72 hour), the concentration that reduced biomass by 50%, was 0.25 mg/L. The E_rC_{50} (0-72 hour), the concentration that reduced specific growth by 50%, was 1.2 mg/L. The No Observed Effect Concentration (NOEC) was 0.048 mg/L. *Based on geometric mean measured test concentration:* The E_bC_{50} (72 hour), the concentration that reduced biomass by 50%, was 0.18 mg/L. The E_rC_{50} (0-72 hour), the concentration that reduced specific growth by 50%, was 0.96 mg/L. The No Observed Effect Concentration (NOEC) was 0.028 mg/L.
Data Quality	(1) Reliable without restriction
References	Vryenhoef & McKenzie. Algae Inhibition Test. SafePharm Laboratories Project No.: 1666/074. 23 Sep 2005.
Other	Updated: 11/17/2005

MAMMALIAN TOXICITY

4.0 Acute Oral Toxicity

Robust Summary 28-Acute Oral –1

Test Substance	
CAS #	CAS# 72624-02-3
Chemical Name	Phenol, heptyl derivatives
Method	
Method/Guideline followed	Similar to FHSA 16 CFR 1500.3
Test Type	Acute oral toxicity
GLP (Y/N)	Y
Year (Study Performed)	1982
Species/Strain	Rats/Sprague-Dawley strain
Sex	Male and Female
No. of animals/dose	5/sex
Vehicle	None
Route of administration	Oral (intragastric)
Dose level	2.0 g/kg
Dose volume	Not provided
Control group included	No
Remarks field for test conditions	A single dose of the undiluted test material was administered intragastrically to five fasted (over night) male and female rats. The animals were observed for signs of toxicity or behavioral changes frequently on the day of dosing and twice daily thereafter. Individual weights were recorded on the day of dosing. Gross autopsies were performed on all animals.
Results	LD50 <2.0 g/kg (males and females)
Remarks	Four of five females died within 24 hours post dosing. The remaining female and all of the males died on days 2 and 3. The animals were ruffled after 3 hours. They had dirty oily coats, appeared depressed and had discharge around the mouth and nose after 24 hours. All animals died prior to the first post dosing weighing interval. At necropsy pale and mottled livers and pale spleens were observed.

Conclusions	The test article, when administered as received to male and female Sprague-Dawley rats, had an acute oral LD50 of <2.0 g/kg (males and females.).
Data Quality	Reliable with restriction (Klimisch Code). Restriction due to the lack of individual animal data in the final report.
References	Unpublished confidential business information
Other	Updated: 5/30/2003

Robust Summary 28-Acute Oral –1

Test Substance	
CAS #	CAS# 72624-02-3
Chemical Name	Phenol, heptyl derivatives
Method	
Method/Guideline followed	Similar to FHSA 16 CFR 1500.3
Test Type	Acute oral toxicity
GLP (Y/N)	Y
Year (Study Performed)	1982
Species/Strain	Rats/Sprague-Dawley strain
Sex	Male and Female
No. of animals/dose	5/sex
Vehicle	None
Route of administration	Oral (intragastric)
Dose level	0.2 g/kg
Dose volume	Not provided
Control group included	No
Remarks field for test conditions	A single dose of the undiluted test material was administered intragastrically to five fasted (over night) male and female rats. The animals were observed for signs of toxicity or behavioral changes frequently on the day of dosing and twice daily thereafter. Individual weights were recorded on the day of dosing, on day 7 and at termination. All animals were euthanized at the conclusion of the observation period. Gross autopsies were performed on all animals after 14 days.
Results	LD50 >0.2 g/kg (males and females)
Remarks	All animals survived the duration of the study. The animals were ruffled after 3 hours. They had dirty coats with urine stains and a bloody discharge around the nose and mouth within 24 hours. Between 12 and 24 hours the animals were vocalizing. The dirty coats and discharge gradually improved and the animals appeared to be recovered by day 3. The males exhibited an 8% decrease in mean body weight during week 1. Male body weights recovered during week 2. Female body weights were unremarkable. Necropsy results were unremarkable.
Conclusions	The test article, when administered as received to male and female Sprague-Dawley rats, had an acute oral LD50 of >0.2 g/kg (males and females.).
Data Quality	Reliable with restriction (Klimisch Code). Restriction due to the lack of individual animal data in the final report.
References	Unpublished confidential business information
Other	Updated: 5/30/2003

4.1 Acute Dermal Toxicity

Test Substance	
CAS #	CAS# 72624-02-3
Chemical Name	Phenol, heptyl derivatives
Method	
Method/Guideline followed	OECD Guideline 402 and EPA Pesticide Assessment Guidelines (November 1982)
Test Type	Acute dermal toxicity (Limit Test)
GLP (Y/N)	Yes
Year (Study Performed)	1985
Species/Strain	Rabbits/New Zealand White
Sex	Male and female
No. of animals/sex/group	5
Vehicle	None
Route of administration	Dermal
Dose level	2 g/kg
Control group included	No
Remarks field for test conditions	Approximately 24 hours prior to topical application of the test material, the hair of each animal was closely clipped. A single dose of 2 g/kg of the undiluted test material was administered dermally to five male and five female animals. The test material was kept in contact with the skin for a period of 24 consecutive hours under a gauze pad and wrapped with an impervious material. The application site was washed clean of residual test material at the end of the 24-hour exposure period. The animals were observed for abnormal clinical signs once or twice/day for 14 days after treatment. Individual body weights were recorded on the day of dosing, weekly thereafter and prior to sacrifice. Gross necropsies were performed on all animals on Day 14.
Results	LD50 > 2.0 g/kg (males and females)
Remarks	No male mortality was observed. One female animal was found dead on day 12. This female exhibited a body weight loss at day 7 as well as diarrhea, signs of dehydration and a lack of formed fecal material in the lower gastrointestinal tract at necropsy. In the males signs of necrosis and severe edema were observed in 5 of 5 animals after unwrapping at 24 hours. Eschar was noted at 48 hours (3/5) and 72 hours (2/5). The eschar began to peel at 7 days. One male exhibited a loss of body weight at 7 and 14 days. In the females signs of necrosis and severe edema were observed in 5 of 5 animals after unwrapping at 24 hours. Eschar was noted at 48 hours (5/5). The eschar began to peel at 8 days. No gross necropsy findings were evident in the males or females that were sacrificed on

	day 14.
Conclusions	The test article, when administered dermally as received to 5 male and 5 female New Zealand white rabbits had an acute dermal LD50 of greater than 2.0 g/kg.
Data Quality	Reliable without restriction (Klimisch Code).
References	Unpublished confidential business information
Other	Updated: 5/29/2003

4.2 Genetic Toxicity:

Robust Summary 28-Gentox-1

Test Substance	
CAS #	CAS# 72624-02-3
Chemical Name	Phenol, heptyl derivatives
Method	
Method/Guideline followed	OECD Guideline 471
Test Type	Bacterial Reverse Mutation Assay
GLP (Y/N)	Y
Year (Study Performed)	1993
Test System	*Salmonella typhimurium* and *Escherichia Coli*
Strains Tested	*Salmonella typhimurium* tester strains TA98, TA100, TA1535, TA1537; TA1538 *Escherichia Coli* tester strain WP2*uvr*A
Exposure Method	Plate incorporation
Test Substance Doses/concentration levels	Initial assay: All *Salmonella* Strains + (S9): 0.05, 0.167, 0.5, 1.67, 5.0 and 16.7 ug/plate All *Salmonella* Strains - (S9): 0.05, 0.167, 0.5, 1.67, 5.0 and 16.7 ug/plate WP2*uvr*A + (S9): 0.167, 0.5, 1.67, 5.0, 16.7, and 50 ug/plate WP2*uvr*A - (S9): 0.167, 0.5, 1.67, 5.0, 16.7, and 50 ug/plate Confirmatory Assay A: TA1538 + (S9): 0.05, 0.167, 0.5, 1.67, 5.0 and 16.7 ug/plate TA1535, 1537, 98, 100 and WP2*uvr*A + (S9): 1.67, 5.0, 16.7, 50, 167 and 500 ug/plate All *Salmonella* Strains - (S9): 0.05, 0.167, 0.5, 1.67, 5.0 and 16.7 ug/plate WP2*uvr*A - (S9): 0.167, 0.5, 1.67, 5.0, 16.7, and 50 ug/plate Confirmatory Assay B: TA1535, 1537, 98 and 100 + (S9): 0.5, 1.67, 5.0, 16.7, 50 and 100 ug/plate WP2*uvr*A + (S9): 0.167, 0.5, 1.67, 5.0, 16.7, 50 and 100ug/plate
Metabolic Activation	With and without (6% S9 fraction mix of livers of Aroclor 1254 pretreated Sprague Dawley rats)
Vehicle	DMSO
Tester strain, activation status, Positive Controls and concentration level	TA98 +S9 2-anthramine 2.5 ug/plate TA98 -S9 2-nitroflourene 5.0 ug/plate TA100 +S9 2-anthramine 2.5 ug/plate TA100 -S9 sodium azide 10.0 ug/plate TA1535 +S9 2-anthramine 2.5 ug/plate TA1535 -S9 sodium azide 10.0 ug/plate TA1537 +S9 2-anthramine 2.5 ug/plate TA1537 -S9 9-aminoacridine 150.0 ug/plate TA1538 +S9 2-anthramine 2.5 ug/plate

	TA1538 -S9 2-nitroflourene 5.0 ug/plate WP2*uvr*A +S9 2-anthramine 2.5 ug/plate WP2*uvr*A –S9 ENNG 2.0 ug/plate
Vehicle Control	DMSO
Statistical Analysis	Mean revertant colony count and standard deviation were determined for each dose point. Statistical analysis was performed as appropriate.
Dose Rangefinding Study	Conducted using tester strains TA1538, TA100 and WP2*uvr*A and ten doses of test material ranging from 0.5to 5,000 ug/plate, duplicate plates/dose without metabolic activation. Cytotoxicity was evaluated.
S9 Optimization Study	Yes
Remarks field for test conditions	In the main study there were two treatment sets for each tester strain, with (+S9) and without (-S9) metabolic activation. Each of the tester strains was dosed with several concentrations of test substance, vehicle controls, and a positive control. Three plates/dose group/strain/treatment set were evaluated. The results of the initial assay were confirmed in two independent confirmatory experiments. 0.1 mL of test material, positive control or vehicle control were added to each plate along with 0.1 mL of tester strain, S9 mix (if needed) and 2.0 mL of top agar. This was overlaid onto the surface of minimal bottom agar in a petri dish. Plates were incubated for 48 hours at 37^{o}C. The condition of the bacterial background lawn was evaluated for cytotoxicity and test article precipitate. Revertant colonies were counted using an electronic colony counter. A positive result was defined as a statistically significant dose dependent increase in the number of revertants with at least one dose level inducing a revertant frequency that is two-fold the level of the solvent control.
Results	The test substance was not mutagenic in this assay with or without metabolic activation.
Remarks	The test material was evaluated in a toxicity prescreen in strains TA1538, TA100 and WP2*uvr*A. Results of this evaluation indicated that the test material produced inhibited growth or complete toxicity in all three tester strains at all dose levels tested (50-5000 ug/plate). The dose range find study was repeated at doses ranging from 0.5 to 167 ug/plate. Doses > 5 ug/plate were toxic in TA1538 and TA100 and in doses > 16.7 ug/plate in WP2*uvr*A. Based on these results the mutagenicity assay was conducted at the concentrations listed above. The test material was soluble at all concentrations tested. In the mutagenicity study, inhibited growth was observed in all tester strains at doses between 0.5 and 16.7 and/or 50 ug/plate with S9, and in TA1538 at 5 and 16.7 ug/plate without S9. Revertant frequencies at all dose levels in all tester strains with and without metabolic activation were less than those observed in the concurrent negative controls. The test material was re-evaluated in a confirmatory assay in all tester strains activation at the confirmatory dose levels listed above (Confirmatory Assay A). The test material was soluble at all concentrations tested. Inhibited growth was observed in all tester strains at the highest two or three concentrations tested with and without metabolic activation. Revertant frequencies at all five dose levels in all *Salmonella* tester strains with metabolic activation, and in all six tester strains

	without activation, approximated or were less than those observed in the concurrent negative controls. A statistically significant, 2.6 fold increase was observed in the revertant frequency of WP2*uvr*A at 1.67 ug/plate. This increase was not dose related. **Based on these confirmatory assay results a second confirmatory assay** (Confirmatory Assay B) was conducted. The test article was freely soluble and inhibited growth was observed in all tester strains at 16.7 and 50 and/or 100 ug/plate with activation. A statistically significant, 2.1 fold increase was observed in the revertant frequency of TA1537 at 16.7 ug/plate. This increase was not dose related. The Study Director considered the slight increases observed in the revertant frequencies of TA1537 and WP2*uvr*A to be random fluctuations of the revertant frequencies. The positive and negative controls for each respective test strain were within acceptable limits.
Conclusions	Under the conditions of this study, the test material was not mutagenic.
Data Quality	Reliable without restriction (Klimisch Code)
References	Unpublished confidential business information
Other	Updated: 7/17/2003

Robust Summary 28-Gentox -2

Test Substance	
CAS #	CAS# 72624-02-3
Chemical Name	Phenol, heptyl derivatives
Method	
Method/Guideline followed	OECD Guideline 473
Test Type	In Vitro Chromosomal Aberration Assay
GLP (Y/N)	Y
Year (Study Performed)	2006
Test System	Human peripheral blood lymphocytes
Exposure Method	Dilution
Test Substance concentration levels	Experiment I 4 hour treatment, 20 hour harvest without activation: 0*, 2.5, 5*, 10*, 20*, 30*, 60 µg/mL 4 hour treatment, 20 hour harvest with activation: 0*, 2.5, 5, 10*, 20*, 30*, 60 µg/mL Experiment II 4 hour treatment, 20 hour harvest with activation: 0*, 10, 20*, 30*, 40*, 50, 60 µg/mL 24-hour continuous exposure without activation: 0*, 5, 10, 20*, 30*, 40*, 50 µg/mL *Concentrations selected for metaphase analysis.
Metabolic Activation	With and without S9 fraction mix of livers of phenobarbitone and ß-naphthoflavone-induced rats
Vehicle	DMSO
Vehicle and Positive Control concentration levels by activation status	Mitomycin C - non-activated test system positive control (0.2 or 0.4 µg/mL) Cyclophosphamide - activated test system positive control (5.0 or 7.5 µg/mL) DMSO – solvent control
Statistical Analysis	Statistical analysis of the percent aberrant cells was performed using the Fisher's exact test.
Preliminary Toxicity Dose Range Finding Assay	Consisted of an evaluation of test article effect on mitotic index. Evaluation performed at 4 hours with and without activation following a 20-hour recovery period, and a continuous exposure of 24 hours without metabolic activation. Concentrations of test material evaluated ranged from 19.5 to 5000 µg/mL.
Remarks field for test conditions	In the main study there were two treatment sets for each concentration of test substance, with (+S9) and without (-S9) metabolic activation. Mitomycin C (positive control) was tested without activation and Cyclophosphamide (positive control) was tested with activation. Two hours prior to harvest the spindle inhibitor, Colcemid, was added to each culture to obtain a final concentration of 0.1 ug/mL. Slides were prepared using Giemsa stain. Two-slides/treatment group were evaluated. Whenever possible, a minimum of 200 metaphase spreads (100 per duplicate treatment condition) were examined and scored for gaps, breaks or rearrangements.

Results	Under the conditions of this study the test material did not induce a statistically significant increase in the frequency of cells with chromosome aberrations in human peripheral blood lymphocytes in the presence and absence of a liver metabolizing system at dose levels that induced acceptable levels of toxicity.
Remarks	In the pilot study visible precipitate was observed in treatment medium at dose levels at or above 156.25 µg/mL (4 hour exposure /20 hour recovery groups) and at or above 312.5 µg/mL (24 hour continuous exposure group). Metaphase cells were present up to 39 µg/mL in all of the exposure groups. Hemolysis was also observed at dose levels ≥ 19.5 µg/mL in the absence of activation and at ≥ 39 µg/mL in the presence of activation. Clear evidence of toxicity was evident in all of the exposure groups. Experiment I At the highest test concentration evaluated microscopically for chromosome aberrations, 30 µg/mL, mitotic inhibition was 73%, relative to the solvent control without activation. At 20 µg/mL with activation, mitotic inhibition was 14%, relative to the solvent control. Experiment II At 40 µg/mL, mitotic inhibition was 55 and 51%, relative to the solvent control in the absence and presence of metabolic activation. The frequencies of cells with aberrations in the test article-treated groups were not significantly increased above that of the solvent control at any dose level with or without metabolic activation. Positive and vehicle controls were within the range of the historical control values.
Conclusions	Under the conditions of this study the test material did not induce a statistically significant increase in the frequency of cells with chromosome aberrations in human peripheral blood lymphocytes in the presence and absence of a liver metabolizing system at dose levels that induced acceptable levels of toxicity.
Data Quality	Reliable without restriction (Klimisch Code)
References	Durward, R. Chromosome Aberration Test in Human Lymphocytes *In Vitro*. SafePharm Report No. 1666/072. 19 October 2005.
Other	Updated: 5/15/06

4.3 Repeated-dose and Reproductive/Developmental Toxicity

4.3.1 Systemic Toxicity

Robust Summary 28 - Systemic- 1

Test Substance	
CAS #	CAS# 72624-02-3
Chemical Name	Phenol, heptyl derivatives
Method	
Method/Guideline followed	OECD 407
Test Type	28-day oral toxicity study in rats
GLP (Y/N)	Y
Year (Study Performed)	2006
Species	Rat
Strain	Sprague-Dawley Crl:CD IGS BR, Approximately 7 weeks of age at initiation of treatment
Route of administration	Oral gavage
Duration of test	28 days of treatment
Doses/concentration levels	0, 50, 150 and 450 mg/kg/day
Dose Formulation Analysis	Analysis performed for dosing solution stability, homogeneity and concentration.
Sex	Males and females
Exposure period	28-day treatment duration
Frequency of treatment	Once daily, 7 days/week
Control group and treatment	10 rats/sex/group in the control and high dose group. 5/sex/group in the low and mid dose group. Control group received daily doses of corn oil at 5.0 ml/kg, and treatment groups received the indicated dose of test material diluted in corn oil at a dose volume of 5 ml/kg
Dose Range find Study	Yes
Post exposure observation period	14-day recovery period in the control and high dose groups.
Statistical methods	Body weight, body weight change, food consumption, continuous functional observational battery (FOB), locomotor activity, clinical pathology and organ weight data were subjected to a parametric 1-way analysis of variance (ANOVA)) to determine intergroup differences. If the ANOVA revealed statistically significant ($p<0.05$) intergroup variance, Dunnett's test was used to compare the test article-treated groups to the control group. Functional observational battery parameters that yielded scalar or descriptive data were analyzed using Fisher's Exact Test.
Remarks field for test conditions	Single oral gavage doses were administered for 28 consecutive days. Clinical examinations were performed twice daily, prior to dose administration and approximately 1 to 2 hours following dose administration. Detailed physical examinations were conducted on all animals weekly, beginning approximately 1 week prior to test article

	administration. A functional observation battery (FOB) was performed prior to dosing during study week three. A full FOB assessment (home cage, removal from home cage handling observations, open field, sensory observations, neuromuscular observations and physiological observations) was performed. All FOB assessments were performed blind. Locomotor activity, recorded after the completion of the FOB, was measured automatically using a Photobeam Activity System. Individual body weights were recorded approximately weekly, beginning approximately 2 weeks prior to test article administration and ending on the days of the scheduled necropsies. Fasted body weights were recorded at necropsy. Individual food consumption was recorded approximately weekly, beginning approximately 2 weeks prior to test article administration and ending on the days of scheduled necropsies. Urinalysis, hematology, coagulation and clinical chemistry parameters were evaluated at termination of treatment. Macroscopic examinations were performed on all animals. Select organs were weighed. Microscopic examination was performed on all tissues from all animals in Groups 1 and 4, at the scheduled necropsies and from all animals found dead. Kidneys, liver and gross lesions were examined from animals in Groups 2 and 3 at the primary necropsy and all animals at the recovery necropsy; the stomach (non-glandular), seminal vesicles and thymus were examined from all males in Groups 2 and 3 at the primary necropsy.
Results	
Remarks	Two test article-related deaths were noted in the 450 mg/kg/day group. One male and one female in the 450 mg/kg/day group died on study day 27. Toxicologically relevant clinical observations in these animals prior to death included decreased defecation, dermal atonia, hypothermia and thinness. A specific cause of death for these animals could not be determined but the deaths were most likely attributed to test article administration. There were no other test article-related deaths. One male in the 150 mg/kg/day group died of an accidental death on study day 28, and one female in the 450 mg/kg/day group died on study day 4, presumably due to some aspect of experimental manipulation, but this could not be confirmed based on the gross and histopathology examinations. All other animals survived to the scheduled necropsies. Test article-related clinical observations in the surviving animals during the dosing period consisted of clear material around the mouth and/or ventral neck and forelimbs, and signs of unkempt appearance (yellow material on various body surfaces including the urogenital

	area) in the 450 mg/kg/day group. Dermal atonia and thinness were noted occasionally in the 450 mg/kg/day group. These clinical signs were not observed during the recovery period. Test article-related lower body weights (up to 14%) were noted in the 450 mg/kg/day males. Lower mean body weight gains were noted in this group during the entire dosing period when compared to the control group. Mean body weights in the 450 mg/kg/day males were still lower (8%) than the control group by the end of the recovery period; although some mean body weight gains were higher during study weeks 4 to 5 and 5 to 6. There were no test article-related effects on food consumption. There were no test article-related effects on home cage, open field, sensory, neuromuscular and physiological observations. Locomotor activity patterns were unaffected by test article administration. There were no test article-related effects on food consumption or hematology parameters. Higher urea nitrogen, creatinine (females only) and alanine aminotransferase were noted in the 450 mg/kg/day males and females and higher aspartate aminotransferase was noted in the 450 mg/kg/day males. During recovery these values returned to normal, except for ALT and AST in males, which remained statistically significantly elevated compared to the control group. Higher urine volume was noted in the 450 mg/kg/day males following treatment but not following recovery. Suspected test article-related necropsy alterations included small seminal vesicles in the 450 mg/kg/day males and enlarged/rough surface of the kidney and small thymus in the 450 mg/kg/day females. Organ weight changes attributed to test article administration in the 450 mg/kg/day groups included increases in liver (males and females) and kidney (females) weights along with decreases in seminal vesicle (males) and thymus (males) weights. Histopathologic findings included vacuolation of the hepatocytes (450 mg/kg/day males and females), squamous hyperplasia of the non-glandular stomach (450 mg/kg/day males), depletion of secretion of the seminal vesicles (450 mg/kg/day males), lymphoid depletion of the thymus (450 mg/kg/day males and females) and hemorrhage of the thymus (50 and 450 mg/kg/day males). After the 14-day recovery period, total recovery from vacuolation of the hepatocytes (females only) and squamous hyperplasia were observed in the female and male groups. All other mentioned histopathologic findings were observed with partial recovery after the 14-day recovery period. The histologic changes in the liver and kidney were considered

	directly related to administration of the test article. The histologic changes in the seminal vesicles and the thymus were considered to be associated with stress, and thus were indirectly associated with administration of the test article. Chemical analysis of dosing solutions confirmed that they were homogeneously prepared and stable at the desired concentrations for up to 3 days at room temperature. Concentration analysis confirmed that the dosing solutions were generally within 15% of nominal concentrations.
Conclusions	Based on the results of this study, systemic toxicity was mainly observed at a dosage level of 450 mg/kg/day as evidenced by lethality, clinical observations (decreased defecation, dermal atonia, hypothermia), lower body weights, serum chemistry changes and several histologic changes (tubular nephropathy in the kidneys, fatty change of the liver, stratified squamous hyperplasia of the non-glandular stomach, thymic lymphoid depletion and hemorrhage and depletion of secretion of seminal vesicles). Therefore, the no-observed-adverse-effect level (NOAEL) for oral (gavage) administration to Crl:CD(SD) rats for 28 consecutive days was 150 mg/kg/day as none of the aforementioned effects occurred at that dosage level.
Data Quality	Reliable without restriction (Klimisch Code)
References	Eapen, A. A 28-day Oral (Gavage) Study of Phenol, Heptyl Derivatives (CAS# 72624-02-3) in Rats (with Functional Oberservational Battery and Motor Activity Determinations). WIL Study No.: 186041. 7 August 2006.
Other	Updated: 8/14/2006;

4.3.2 Reproduction/Developmental Toxicity

Test Substance	
CAS #	***CAS# 140-66-9***
Chemical Name	Para-tert-Octylphenol
Method	
Method/Guideline followed	EPA OPPTS Guideline 870.3800
Test Type	Oral (Dietary) Two-Generation Reproductive Toxicity Study
GLP (Y/N)	Y
Year (Study Published)	1999
Species	Rat
Strain	Sprague-Dawley CD rats
Route of administration	Oral by dietary administration
Duration of test	Through F2 weanlings
Doses/concentration levels	0, 0.2, 20, 200 and 2000 ppm
Vehicle control	***Acetone***
Sex	***Males and Females***
Frequency of treatment	Continuously via the diet
Analytical confirmation of concentration.	Homogeneity, stability and periodic dose concentration analysis confirmed that the test material was homogeneously prepared in the diet, was stable in the diet for the period of use, and was at the appropriate concentrations.
Control and treatment groups	30 F_0 rats/sex/group
Mating	Following a 10 week premating period the animals were mated (1 male to 1 female) from the same group for 14 days.
Statistical methods	The unit of comparison was the male, the female, the pregnant female, or the litter, as appropriate. Quantitative continuous data were analyzed using Bartlett's Test for homogeneity of variances followed by appropriate intergroup comparisons (ANOVA; Dunnett's,) and a test for linear trend (Jonckheere. Frequency data were analyzed for differences among treatment groups by Chi-Square Tests followed by Fisher's Exact Test for intergroup comparisons and a test for linear trend. Comparisons for developmental landmarks (e.g., acquisition of vaginal patency and preputial separation) were made using the Mann–Whitney *U* Test. In addition, acquisition of reproductive landmarks was analyzed by analysis of covariance, with body weight as the covariate (the actual body weight on the day of acquisition for selected F1 and retained F2 offspring), and the Least Squares Means Test for pairwise comparisons to the control group value.
Dose rangefinding study	Exposure to the test material at 0, 500, 1000, or 2000 ppm began when the females (five/group) were approximately 6–7 weeks old to approximate the age at onset of exposures in the subsequent multigeneration study, and when additional females (six/group) were sperm-positive and approximately 16–17 weeks old to approximate the age of the females at the time of mating in the subsequent multigeneration study. Duration of exposure was 21 days.

Remarks field for test conditions	**Two-Generation Study** A total of 300 (150 males and150 females) CD rats was assigned to the study at the initiation of the F0 10-week prebreeding test material exposure period. Each group consisted of 30 males and 30 females to yield at least 20 pregnant females/group at or near term. Clinical signs for toxicity, body weights, and feed consumption were monitored. For the last 3 weeks of the prebreeding exposure period, vaginal smears for estrous cyclicity and normality were taken for all F0 females. The animals were mated (1:1) following the 10-week prebreeding exposure period, for 14 days, with no change in mating partners. On postnatal day (pnd) 4, the size of each F1 litter was adjusted to ten pups by eliminating extra pups by random selection to yield, as nearly as possible, five males and five females per litter. On pnd 21, each litter was weaned, and at least one F1 male and one F1 female pup per litter, if possible, were randomly selected (30/sex/group) to produce the F2 generation. Following this selection, three weanlings/sex/litter, if possible, were randomly selected for necropsy. Selected animals of the F1 generation were administered the test material in the diet at their respective dose levels for 10 weeks and then mated to produce the F2 generation following the same study design as described for the F0 generation. Selected weanling females of the F2 generation (30/group) were administered the test material in the diet until acquisition of vaginal patency, then all were terminated. To allow for evaluation of sperm parameters, selected F2 weanling males (30/group) were maintained through acquisition of preputial separation and until 111 $\pm$ 5 days of age. Selected F1 and F2 weanling animals, all F0 and F1 parental animals, and retained F2 male offspring received a complete gross necropsy. The stage of estrus at necropsy was determined for all F0 and F1 females. For weanling animals, the brain, spleen, thymus, ovaries, uterus with cervix and vagina, testes, epididymides, and seminal vesicles were weighed. For parental animals (and retained F2 male offspring) the brain, liver, kidneys, adrenal glands, spleen, ovaries, uterus, testes, epididymides, seminal vesicles with coagulating glands, and the prostate and dorsal prostate were weighed. Specific attention was focused on the examination of the parental reproductive organs, including determining the weight of the prostate and dorsal prostate for all males and ovarian follicle counts for high dose and control F0 and F1 females. At the time of sacrifice of F0 and F1 parental males and retained F2 male offspring, testicular homogenization-resistant spermatid head count and calculation of daily sperm production and efficiency of daily sperm production were determined from one frozen testis/male for all males. In addition, number, motility, and morphology of sperm from one cauda epididymis were evaluated in these same animals. Histopathologic evaluation of the ovaries with oviducts, testis, vagina, epididymis, uterus with cervix, seminal vesicles, and prostate was conducted on the F0 and F1 parental animals and retained F2 male offspring from high dose and control groups.

Results	*Dose Range-Finding Study* For nonpregnant animals, only minimal reductions in body weight and feed consumption were observed at any dose during the 21-day exposure period. Mean intake of test material at 500 ppm was 44 mg/kg/day, at 1000 ppm was 92 mg/kg/day, and at 2000 ppm was 203 mg/kg/day. For pregnant animals, (gestation days 0–21) mean intake at 500 ppm was 32 mg/kg/day, at 1000 ppm was 64 mg/kg/day, and at 2000 ppm was 149 mg/kg/day. Similar to the nonpregnant animals, only minimal effects were observed at any dose during the dosing period. All six females per group, designated to be pregnant, were pregnant. None were removed from study or died while on study. Two (of six, 33.3%) at 2000 ppm carried fully resorbed litters at scheduled sacrifice on gestation day 21; all remaining dams had live litters at scheduled termination. The relationship of these findings to treatment was unclear. In historical control data from the performing laboratory for over 350 confirmed pregnant females, none had fully resorbed litters. On the other hand, no effects of any magnitude were observed in the fetuses from the four females at 2000 ppm that did not resorb their litters. There was no evidence of increased prenatal deaths (e.g., resorptions or fetal deaths) at 1000 ppm. Based on all of these considerations and the preliminary nature of the study, the resorptions could not reliably be ascribed to treatment with the test material. In the definitive study there were no treatment-related increases in prenatal (or postnatal) deaths, including no changes in resorption rates after in utero exposure to the test material at dietary concentrations over four orders of magnitude. Therefore, the resorptions observed in the range-finding study were clearly not related to test material toxicity. **Dose Selection for the Two Generation Study** In discussions with the U.S. EPA, the target dietary doses selected for the two-generation study were: 0, 0.2, 20, 200, and 2000 ppm. The rationale was: A) For the high dose region, test substance intake of parental animals would be just below, at, or above levels previously shown to saturate liver metabolic capacity (200 mg/kg/day), and intake of young animals would exceed this dose. B) 2000 ppm would be expected to result in decreased body weight and possible other effects, thus providing an appropriate high dose. C) 2000 ppm would allow for evaluation of whether the spontaneous resorptions observed in the probe study at this dietary concentration were related to test material toxicity. D) The low dose (0.2 ppm) provided for daily intake of the test material between two doses that purportedly caused effects on sperm count and testicular weight in an earlier study. E) The 20 ppm dose was considered adequate support for the low dose evaluation if bioavailability of the test material was lower due to dietary exposure compared to drinking water exposure used in the prior study. *Two Generation Study* Test substance consumption in the 0.2, 20, 200, and 2000 ppm groups ranged from 0.034–0.011, 3.3–1.05, 32.6–10.9, 369–111 mg/kg/day, respectively, depending on the age and sex of the animals and the phase of the study; e.g.,

consumption was highest for weanlings and for dams during lactation.

Parental Systemic Parameters
Treatment-related effects were limited to consistent and persistent reductions in body weights and weight gains in both sexes in the F0, F1, and F2 generations at 2000 ppm. Feed consumption in g/day and g/kg/day did not exhibit any persistent or consistent treatment-related effects for either sex in any generation. There were no treatment- or dose-related clinical observations in either sex in any of the generations. Body weights during gestation were unaffected and were reduced during lactation in F0 and F1 females at 2000 ppm There were no effects on these parameters at 0.2, 20, or 200 ppm. At necropsy, F0 and F1 parental and F2 retained male absolute organ weights were almost uniformly unaffected for liver, kidneys, adrenal glands, spleen, and brain. Relative organ weights were similarly unaffected, and occasional differences from control were not considered biologically significant (not consistent from generation to generation, absolute organ weights were unaffected, and changes in body weights were the basis for the changes in relative organ weights, etc.). There were no treatment- or dose related gross or microscopic findings for the examined organs, for F0 and F1 parental animals, and for F2 retained adult males.

Parental Reproductive Parameters
There were no treatment-related effects in F0 or F1 females on mating, fertility, pregnancy, gestational indices, number of implants, total pups, live or dead pups per litter, percentage post implantation loss (prenatal mortality index), or gestational length (in days). Estrous cycle length in days and stage of estrus at necropsy were equivalent across all groups. There were no treatment-related effects on absolute or relative reproductive organ weights or on gross or histological examinations of the reproductive organs. Paired ovarian follicle counts were similar between high dose and control F0 and F1 females. There were no effects of treatment in F0 or F1 males on mating or fertility indices. There were also no treatment-related effects in F0, F1, and retained F2 males on absolute or relative weights of the testes, epididymides, prostate, dorsal prostate, or seminal vesicles plus coagulating glands, and no effects on epididymal sperm concentration, percentage motile or progressively motile sperm, testicular homogenization-resistant spermatid head counts, daily sperm production, or efficiency of daily sperm production. Percentage abnormal sperm was also unaffected for parental F0 and F1 males and for retained F2 males. The elevated values for F1 males at 0 ppm (6.1%) and 0.2 ppm (5.2%) were each due to a single male per group with few or no motile sperm and most or all abnormal sperm; in both cases they sired live litters. There were no treatment-related gross or microscopic findings on reproductive organs for F0, F1, or F2 adult males.

Offspring Parameters
Pup body weights per litter were reduced at 2000 ppm for both F1 and F2 offspring at pnd 14 and 21. Organ weights at weaning showed some differences from the control, although these differences were not considered biologically

	significant (some were increased, some were decreased, they were not consistent from generation to generation, they did not persist to adulthood, etc.) and/or due to decreased body weights. The mean age of acquisition of vaginal patency in F1 females ranged from 30.5 to 31.8 days, with the mean body weight at acquisition ranging from 97.83 to 91.91 g. The mean age of acquisition of preputial separation in F1 males ranged from 43.1 to 44.7 days, with the mean body weight at acquisition ranging from 220.07 to 207.01 g. Age at acquisition of vaginal patency was significantly delayed at 20 ppm (31.9 days) and 2000 ppm (31.8 days) relative to the control value (30.5 days), and the age at acquisition of preputial separation was significantly delayed at 2000 ppm (44.7 days) relative to the control group value (43.1 days). F1 female body weight at acquisition exhibited a significant dose-related downward trend with the mean weight at 200 ppm, 206.09 g (but not at 2000 ppm, 207.01 g) significantly reduced relative to the control value, 220.07 g. When the age at acquisition was statistically analyzed by analysis of covariance, with body weight as the covariate, only the ages at acquisition of vaginal patency and preputial separation at 2000 ppm were significantly delayed from the control group values. Body weights of pups by sex by litter on pnd 0 were equivalent across all groups for male and female F1 pups. The same statistically significant minor delays in vaginal patency were observed at 2000 ppm in F2 females (31.3 days) versus the control value (30.6 days), and in preputial separation at 2000 ppm in F2 males (43.6 days) versus the control value (42.2 days), with no statistically significant effects on body weights at acquisition. Body weights of pups by sex by litter on pnd 0 did not differ among groups for either male or female F2 pups. The statistically significant effect on acquisition of reproductive landmarks in F1 offspring required measurement of anogenital distance in newborn (pnd 0) F2 offspring. Anogenital distance in males was equivalent across all groups, with F2 male pup body weights per litter also statistically equivalent across all groups. Anogenital distance in the newborn F2 females was significantly longer in all test material-exposed groups, with mean values of 0.79, 0.81, 0.85, and 0.79 mm at 0.2, 20, 200, and 2000 ppm, respectively, compared to the control mean value of 0.76 mm, with no significant differences among groups for female body weight/litter at birth.

Conclusions	Dietary exposure to para-tert-Octylphenol for two generations, one litter per generation at 0, 0.2, 20, 200, and 2000 ppm, resulted in effects only at 2000 ppm. The effects included decreased body weights and weight gains in adults, reduced body weight during the latter portion of lactation in offspring, and slightly delayed vaginal opening and preputial separation, considered related to body weight decreases. No effects on reproductive parameters, testes weights or morphology, epididymal sperm counts, motility, or morphology, daily sperm production, efficiency of daily sperm production, or prostate or dorsal prostate weights or histopathology were observed. No estrogen like effects on males or females and no low dose effects were evident. The NOAELs for systemic and postnatal toxicity were 200 ppm and for reproductive toxicity was at or above 2000 ppm.
Data Quality	Reliable without restriction (Klimisch Code)
References	Tyl RW, *et al.* Two-generation reproduction study with para-tert-octylphenol in rats. Regulatory Toxicology and Pharmacology 30 (2 Pt 1), 81-95 (1999)
Other	Updated: September 15, 2006